This guidance was written prior to the February 27, 1997 implementation of FDA's Good Guidance Practices, GGP's. It does not create or confer rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both. This guidance will be updated in the next revision to include the standard elements of GGP's.

REVIEW CRITERIA FOR ASSESSMENT OF IN VITRO DIAGNOSTIC DEVICES FOR DIRECT DETECTION OF CHLAMYDIAE IN CLINICAL SPECIMENS

This is a flexible document representing the current major concerns and suggestions regarding in vitro diagnostic devices employing immunochemical or other methodologies for direct detection of chlamydiae in clinical specimens. It is based on 1) current basic science, 2) clinical experience, 3) previous submissions by manufacturers to the FDA, and 4) the Safe Medical Devices Act of 1990 (SMDA) and FDA regulations in the Code of Federal Regulations (CFR). As advances are made in science and medicine, these review criteria will be re-evaluated and revised as necessary to accommodate new knowledge.

PURPOSE: The purpose of this document is to provide guidance on information to present to the Food and Drug Administration (FDA) before a device to detect chlamydiae directly in clinical specimens may be cleared for marketing.

DEFINITION: This generic type device is intended for use in clinical laboratories* as an in vitro diagnostic test for qualitative measurement of chlamydiae directly in clinical specimens by immunochemical and other methodologies.

* Devices may be cleared for use in physician office laboratories when additional data is submitted to demonstrate equivalent performance in these settings.

PRODUCT CODE(S):

LSK	Chlamydia, DNA reagents
LJC	ELISA, Chlamydiae group
LKI	Antisera, fluorescent, Chlamydia spp.
LKH	Antisera, immunoperoxidase, Chlamydia spp.

REGULATION NUMBER: 21 CFR § 866.3120

CLASSIFICATION: I

PANEL: MICROBIOLOGY (83)

REVIEW REQUIRED: Premarket Notification [510(k)]

I. CLINICAL INDICATION/SIGNIFICANCE/INTENDED USE OF CHLAMYDIAE DETECTION DEVICES

Chlamydiae are an obligate intracellular group of gram-negative bacteria which are genetically diverse but similar in morphology, intracellular developmental cycle, and antigenic properties. Chlamydiae can only be propagated in cell-culture systems due to dependency on host cells for the manufacture of high energy

adenosine triphosphate metabolites. The developmental cycle includes two major forms: the infective nondividing elementary body that can survive extracellularly, and the noninfective reticulate body that divides intracellularly by binary fission.

Chlamydiae are the etiologic agents of a wide spectrum of adult, adolescent, and pediatric infections which affect diverse anatomic sites.[1] Advancements in diagnosis and management of chlamydial disease requires reliable laboratory methods for detection.

Chlamydia trachomatis is a major cause of sexually transmitted diseases [lymphogranuloma venereum (LGV), nongonococcal urethritis (NGU), cervicitis, and ascending infections of the female genital tract], inclusion conjunctivitis, and infant interstitial pneumonia. The majority of uncomplicated genital infections may be asymptomatic or have symptoms that are not specific. Laboratory diagnosis is essential for treatment and epidemiological control of the disease. Complications of untreated infections in men are not common; however, inapparent infections serve as a reservoir of infection. Many infected women develop ascending infections with major sequelae including infertility due to tubal occlusion, ectopic pregnancy, and chronic pelvic pain. Infants may be infected at birth, causing conjunctivitis, otitis media, pharyngitis or pneumonitis. Neonatal chlamydial conjunctivitis is more common than gonococcal ophthalmia neonatorum. Chlamydial eye infections in older children and adults must be differentiated from other infective and noninfective causes of conjunctivitis and keratoconjunctivitis. Endemic trachoma is a chronic disease caused by repeated conjunctival and corneal infections with C. trachomatis; it is the most common cause of preventable blindness world-wide.[2]

C. pneumoniae, previously designated the TWAR (Taiwan-Acute Respiratory) agent is associated with pneumonitis, bronchitis, and pharyngitis; reinfection is common.[3] C. psittaci may be the cause of accidental infections from birds and infrequently from sheep. It typically produces an atypical pneumonia, but rare infective endocarditis and human infections resulting in abortion have also been reported.[4]

Human isolates of C. trachomatis are grouped into trachoma (serovars A-K) and LGV biovars (serovars L1, L2, and L3). Trachoma biovar strains preferentially infect columnar epithelial cells while LGV biovar strains cause systemic infection of reticuloendothelial tissue. In cell culture, avian C. psittaci and LGV strains of C. trachomatis are readily ingested by many cell lines and undergo multiple cycles of infection and replication, increasing organism yield in laboratory propagation. Trachoma biovar strains of C. trachomatis require centrifugation to increase efficiency of cell line ingestion. The inclusions of C. trachomatis have glycogen deposits and can be distinguished from C. psittaci in infected cells by iodine staining. Isolation

of C. pneumoniae has been difficult; use of HeLa 229 cell cultures with staining by genus-specific monoclonal antibody and failure to stain with iodine and a C. trachomatis species-specific monoclonal antibody has been described.[5]

By use of monoclonal antibodies, biological properties, and DNA hybridization, C. trachomatis has been divided into antigenically related serovars,[6] that are predominantly associated with different diseases[1]:

A, B, Ba, C	Hyperendemic blinding trachoma
D-K	Urethritis, cervicitis, endometritis, salpingitis, perihepatitis, epididymitis, proctitis, "acute urethral syndrome", inclusion conjunctivitis, infant pneumonia
L1, L2, L3	Lymphogranuloma venereum

Although chlamydiae are antigenically complex, only a few antigens are used in laboratory diagnosis.[7] All chlamydiae have an antigenic group-reactive lipoprotein-polysaccharide complex (LPS) which is soluble, heat-stable, and resembles gram-negative endobacterial lipopolysaccharide but with a unique determinant.[4] The 40 kD major outer membrane protein (MOMP) possesses genus-, species-, subspecies- and serovar-specific determinants. A 60 kD cysteine-rich outer membrane protein also possesses genus-, species-, and biovar-specific epitopes and has been used for DNA sequence comparisons.[8]

Chlamydial infections may be diagnosed by:

1) Direct microscopic examination of stained clinical material; Giemsa, Papanicolaou, and other tissue stains have been used, but are not recommended due to insensitivity for diagnosing chlamydial infections other than neonatal conjunctivitis.

2) Direct immunofluorescence microscopy (DFA); these methods also allow evaluation of specimen quality, but are generally not suited to testing large numbers of specimens and require experienced microscopists.

3) Direct detection of chlamydial antigen by enzyme immunoassays; these methods do not allow evaluation of specimen quality, but facilitate processing of large numbers of specimens.

4) Nucleic acid hybridization; these methods are similar to direct antigen detection tests in sensitivity and specificity, and also do not allow evaluation of specimen quality.

5) Isolation in cell culture using morphological or immunological identification of characteristic inclusions.

Currently, legally marketed devices for the direct detection of chlamydiae are available from various manufacturers and use the following technologies:

1) DFA directed against species-specific MOMP or genus-specific LPS of the organism.

2) Enzyme immunoassays using polyclonal and/or monoclonal antibodies directed against chlamydial LPS and/or MOMP in a microtiter or membrane format.

3) Nucleic acid hybridization.

Not all specimen types are acceptable for all three direct technologies. Testing of specimens from the following sites have been cleared:

1) female endocervix using swab or cytobrush collection;

2) male urethral swab, and first catch or first morning urine;

3) infant conjunctiva using swab collection; and

4) infant nasopharynx using aspirate or swab collection.

Isolation in cell culture remains the "gold standard" for detection of chlamydiae. Although the sensitivity is less than 100% (estimated at 80 to 90 percent),[9] a positive result is 100% specific when performed by competent laboratories. The recommended method for culture of C. trachomatis is performed using McCoy cells treated with cycloheximide, with blind passage of negative cultures at 72 to 96 hr.[7] Staining of the cell monolayer with a species-specific monoclonal immunofluorescent antibody[10] is more sensitive and detects inclusions earlier than iodine or Giemsa staining. Other modifications to the shell vial procedure originally described by Ripa[11] have been described using microdilution plates.[12] Quantitative culture methods have been described which determine inclusion-forming units (IFU) per well or milliliter of transport medium.[13] For research purposes and epidemiological studies, isolates of C. trachomatis may be serotyped by the microimmunofluorescent technique.[7]

Factors affecting efficiency of cell culture include the type of swab used, type of specimen, number of swabs collected, order of swab collection, transport conditions, length of transport time, and culture variables such as centrifugation speed and time, use of microdilution plates or shell vials, blind passages, and use of vortexing or sonication.[14] Quality control procedures should be applied to both specimen collection and chlamydial isolation to

ensure optimum recovery in the system used.[15] Cell culture may be only 80 to 85 percent sensitive when a single endocervical specimen is tested[16] and any modifications to the recommended McCoy cell monolayers in vials, using centrifugation, and immunofluorescent staining, will result in lower isolation rates. In any comparative study, using a reference cell culture method of poor sensitivity will inappropriately indicate a higher sensitivity of the non-culture method.

II. DEVICE DESCRIPTION

Key issues in the 510(k) review of a new device are the specific intended use (the analyte detected and the indications for use), the type of specimen collected, and the technology utilized. The following descriptive information must be included in a 510(k) submission to adequately characterize the new in vitro device for detection of chlamydiae directly in clinical specimens. Appropriate literature references that have been subjected to peer review and package insert(s) for another similar commercial test assay(s) must be attached.

A. Intended Use.

Describe the intended use based on the technology/methodology employed in the device. The following questions should be addressed:

1. What patient populations should be tested?

2. What are the conditions and limitations of use of the device when used to diagnose specific chlamydial infections directly from clinical specimens?

B. Detailed Principle of the Test Methodology.

Discuss the principle of the test methodology(ies) and whether the methodology is well-established and well-proven. For new technologies, provide information to substantiate application of the methodology to the detection of chlamydiae. Cite literature references where appropriate. Describe similarities and differences in technology and design of the new device as compared to a device of similar technology and design that is legally marketed in the United States. Include a complete description of the following components if appropriate:

1. Extraction/pretreatment procedure.

2. Detecting and/or capture antibody and what antigen(s) or epitope(s) are detected; for nucleic acid hybridization methods, the nature of the probe utilized and its target sequences.

3. Conjugate.

4. Enzymatic, fluorescent, or other substrate used to detect antigen-antibody complexes.

5. Blocking antibody and its specificity, if included for confirmation of positives.

6. Determination of the cut-off value(s) or endpoint(s) for the assay; for new technologies, this may be validated using data as described in III.A.1.

7. Controls/calibrators included in the assay kit and what aspects of the procedure are verified.

8. Any additional reagents or methods which contribute to the effectiveness of the device.

9. Collection and transport materials provided in the kit or recommended for use.

10. Software elements and dedicated instrumentation that are responsible for specimen handling and/or that are used in calculating assay results. See requirements for Minor Level of concern in Reviewer Guidance for Computer Controlled Medical Devices Undergoing 510(k) Review (available from the Division of Small Manufacturers Assistance).

C. Merits and Limitations of the Methodology(s).

Discuss the merits and limitations/advantages/disadvantages of the test methodology(ies) of the new device compared to other available test methodologies.

D. Specimen Type(s).

List all specimen types/matrices indicated for use with the new device.

III. SPECIFIC PERFORMANCE CHARACTERISTICS

The FDA requests different types and amounts of data and statistical analyses to market in-vitro diagnostic devices. The amount and types of data requested depend on the intended use and the technological characteristics of the new device. The data and statistical evaluation should be sufficient to determine if the device is substantially equivalent to a legally marketed device and/or safe and effective for all claimed specimen type(s). Additional data may be necessary to substantiate certain claims of intended use or clinical significance, or to validate use of a new technology.

All protocols for in vitro testing should be clearly stated. Test data should be presented with analyses and conclusions. Results should be summarized and include explanations provided for unexpected results and any additional testing performed. When appropriate, charts (scattergrams, histograms, ROC curves, etc.) may be used as part of analyses and conclusions. Raw data may be requested.

Submission of the following data is required to determine the ability to detect chlamydiae using immunochemical or hybridization methodology:

A. Analytical Laboratory Studies.

Specific parameters of importance to the operation of the device should be supported by data determined with the device prior to testing in outside laboratories. Testing should be done in-house or at a designated laboratory facility as part of the test development phase.

1. Validation of Cut-off

Describe the rationale for determination of the assay cut-off(s).

For new technologies, data should demonstrate that the cut-off has been appropriately selected by testing the following:

a. A minimum of 100 positive endocervical swab specimens* determined by culture and including specimens with fewer than 100 IFU/mL in culture.

b. A minimum of 100 endocervical swab specimens* determined to be negative by culture.

* Frozen specimens may be used if a subset is compared to testing fresh specimens.

Resolution of discrepancies may use other methods as for comparison studies (see III.B.).

2. Antiserum or Probe Specificity

The specificity of the new device for detecting chlamydiae or a particular species should be demonstrated as completely as possible. The cross-reactivity should be investigated using the assay system. Strains of the following microorganisms should be tested for cross-reactivity in addition to those that would be encountered as pathogens or normal flora in the patient specimen types which will be tested:

Salmonella typhimurium
Salmonella minnesota
Staphylococcus aureus, protein A-producing strain
Peptostreptococcus productus
Neisseria gonorrhoeae
Acinetobacter spp.
E. coli
Klebsiella pneumoniae
Gardnerella vaginalis
Group B beta streptococcus
Group A beta streptococcus
Proteus mirabilis
Moraxella lacunata
Haemophilus influenzae

For urogenital sites include:

Mycoplasma hominis
Ureaplasma urealyticum
Herpes simplex 1 and 2
Trichomonas vaginalis
Candida albicans
Candida glabrata

For urine specimens include: 50 patient specimens with bacterial culture confirmed urinary tract infections.

For C. trachomatis species-specific assays:
C. pneumoniae
C. psittaci

Cross-reactivity studies should use suspensions of the microorganisms diluted in the transport or storage medium recommended or included in the test kit. Perform colony counts or tissue culture to verify that a minimum of 10^6 CFU/mL or 10^6 PFU/mL are tested.

3. Limits of Detection.

The analytical sensitivity (limits of detection) of the assay should be determined using cultured Chlamydia spp. Dilute harvested cells independently in transport media recommended in the assay procedure to simulate low to moderate numbers of infective units (or elementary bodies).[15] All serovars of C. trachomatis, C. psittaci, and C. pneumoniae should be similarly tested in triplicate for each dilution. Present data as lowest dilution and IFU (or equivalent) per mL and specify method of quantitation. Specify method of calculating IFUs.

4. Interference Studies.

Any potentially cross-reacting or interfering substances potentially encountered in specific specimen types or conditions should be tested using the assay system, e.g., storage conditions, presence of blood, mucus, freeze-thawing, etc.

This would include but not be limited to spermicides, lubricants, talcum powder, ophthalmic ointments, etc. Alternatively, a statement may be added to the Limitations section of the package insert that *** assay has not been tested for cross-reactivity or interference.

Verify that recommended storage conditions are compatible with the assay. State the optimal conditions based on specimen storage stability studies. Both false positivity and false negativity should be evaluated.

5. Reproducibility

The National Committee for Clinical Laboratory Standards (NCCLS) recommends an analysis of variance experiment that permits estimation of within-run and total standard deviations (SD).[17] See EP5-T2 (NCCLS Guideline) for recommended data collection formats and calculations. Perform separate calculations for each specimen tested for within-run and total precision.

For all test formats, test a minimum of two negative, two low positive (less than 100 IFU/mL), and two moderately high positives (100-1000 IFU/mL) in addition to controls included in the assay kit, three times in each of two runs on three different days. Specimens may be spiked specimens prepared by adding the specimen to diluted transport media or specimen diluent.

Reproducibility studies should also be done on the same specimens at the two outside laboratories performing comparative studies, in addition to the manufacturer's laboratory. Controls contained in the test kit should also be included.

For calculated endpoint tests, present coefficients of variation for each set of values for with-in run and total precision, using absorbance values and reporting units defined in the test procedure.

For single endpoint assays, provide percentage of results negative, borderline/equivocal, or positive for each set of tests.

For tests designed to be marketed in physician office laboratories, at least 10 different samples representing negative, low positive, and high positive specimens should be aliquoted, coded, blinded, and tested at 3 different physician office locations. Testing should be performed by office personnel who would perform the tests in these settings and compared to results obtained in a clinical laboratory setting.

If dedicated instrumentation is used in specimen handling, or reading and interpreting results, use a different instrument at each site. If non-dedicated instruments are used, state specifications of instrument(s) used at each site.

B. Comparison Studies.

Comparison studies provide data on the ability of the system to accurately detect chlamydiae. It should be demonstrated that the performance of the device is substantially equivalent to another similar legally marketed chlamydial assay by comparison to a well-controlled cell culture method at minimally two different clinical sites with different infection prevalences. A justification for choice of culture methods, including pertinent references and procedure protocols should be included in the submission. The culture method used should be clearly described, including specimen collection methods, types of swabs used, transport media used, transit time between collection and culture, storage conditions prior to culture, and specific laboratory culture procedures, including quality control procedures performed and methods of quantitation. Include in data presentation the number of cultures positive only after blind passage* and the number of inclusions detected per coverslip or well. Another legally marketed assay may also be included in the comparison(s) data.

* Blind passage is necessary when iodine or Giemsa staining rather than fluorescent antibody staining is used to identify inclusion bodies.

The new device under evaluation should be similarly described and should conform to procedures and recommendations specified in the product insert. If discrepancies are found and persist upon repeat testing (all borderline/equivocal results should be similarly repeated), a DFA stain with monoclonal antibodies on the spun sediment of the transport (or holding) media, an ELISA method confirmed by a monoclonal blocking antibody, subpassage of negative cultures, repeat cultures, and/or clinical chart review for clinical or epidemiological information may be used for resolution. When other nonculture methods are used for resolution, they should

measure different chlamydial properties or antigens (e.g., using a MOMP species-specific monoclonal vs. a genus-specific polyclonal antibody detection system or a DNA/RNA hybridization technique).

Provide package inserts for any commercially available assays tested in parallel or used to resolve discrepancies. Provide the names and telephone numbers of principal investigators and sites at which testing was performed. Comparative testing should be performed by at least two independent investigators at separate independent locations.

The tests should be performed on an adequate number of positive and negative clinical specimens (following collection, storage, and testing instructions recommended in the package inserts), and the relative sensitivity and specificity declared in the PERFORMANCE CHARACTERISTICS section of the package insert. The following are minimum recommended sample size populations for comparison testing of different specimen types:

1. Female endocervical swab specimens

   a. High risk population (greater than 15% prevalence); n=300.

      This population may be defined as patients attending STD clinics, sexually active patients less than 25 years of age, women with confirmed N. gonorrhoeae infection, and/or those exposed to a partner with an STD.

      Document symptomatic (e.g., presence of mucopurulent endocervical discharge) and asymptomatic patients; define criteria used. If a patient is diagnosed with another STD (N. gonorrhoeae, T. vaginalis, G. vaginalis, etc.), indicate other laboratory findings.

   b. Low risk population (less than 5% prevalence); n=300.

      This population may be defined as women attending private or public obstetrics and gynecology practices without symptoms or with mild nonspecific symptoms, and not falling into a high risk group defined in 1.a.

2. Male urethral swab specimens.

a. Symptomatic patients attending an STD clinic or other facility specifically for symptoms of urethritis or epididymitis, those with exposure history, or those with pyuria or 5 or more polymorphonuclear leukocytes per high-power field on a urethral Gram stain; n=150.

b. Asymptomatic patients attending an STD clinic or other facility not defined as in 2.a.; n=150.

3. Male first morning or first catch urine specimens

a. Symptomatic patients*; n=150.

b. Asymptomatic patients*; n=150.

* Perform chlamydial culture on both a urethral swab specimen and a urine specimen collected at the same time.

4. Conjunctival swabs.

Infants/neonates born to mothers with proven chlamydial cervicitis or infants with conjunctival discharge; n=100.

To extend clinical utility to adults and older children, include 100 such patients with conjunctival discharge.

Document positive results from bacterial and viral cultures. Specimens should include those from which other agents have been isolated. At least 30 patients positive for C. trachomatis should be included.

5. Nasopharyngeal swabs or aspirates from infants/neonates suspected to have pneumonia; n=200.

Document symptomatic and asymptomatic patients and isolation of other respiratory pathogens diagnosed as agents of pneumonia by bacterial or viral cultures. At least 30 patients positive for C. trachomatis should be included.

IV. LABELING CONSIDERATIONS

The following are additional details for some of the points in the statute [502(f)(1)] and regulations [21 CFR § 809.10(b)].

A. The Intended Use Statement

The intended use statement should be a concise description of the essential information about the product. It should communicate the following information:

1. Test methodology.

2. Whether the assay detects a specific chlamydial species or whether the assay detects chlamydial genus.

3. What specimen sources may be tested.

4. If the assay is to be used only with a special instrument.

A typical intended use statement is: *** test is for the detection of [C. trachomatis/chlamydiae] using the ABC automated system for male urethral and urine, female endocervical, and infant conjunctival swab specimens.

B. Conditions for Use

Conditions for use of the device should describe any special applications of the device or specific contraindications or indications for use not addressed in the Intended Use Statement, e.g., for nasopharyngeal swabs only from infants as an aid in the diagnosis of chlamydial infant pneumonia.

These conditions for use may be addressed further in either the Summary and Explanation, Limitations, or Performance Characteristics Section of the package insert.

C. Specimen Collection and Handling

1. State the type of specimen to be collected, and the types of collection devices which may be used.

2. State the conditions for patient preparation, e.g., timing of collection, order of collection, etc.

3. Provide adequate directions for sample collection and/or references for appropriate collection procedures, e.g., textbooks, journals, etc.

4. Identify interfering substances or conditions.

5. Provide instructions for inoculating transport media or other methods to transport to the laboratory for testing.

6. State the specimen storage conditions and stability periods.

D. Quality Control

Information provided in a Quality Control section should include the following information:

1. State which ATCC organisms or commercially available products should be used for positive and negative quality control, if materials are not provided in the kit. Advise user if controls provided challenge all aspects of the procedure and recommend alternative control measures to challenge those steps not covered.

2. Provide recommendations for frequency of quality control.

3. Provide directions for interpretation of the results of quality control samples.

4. The Quality Control section should conclude with a statement similar to the following: "If controls do not behave as expected, results are invalid and patient results should not be reported".

E. Expected Results

1. Reference expected prevalence of chlamydial infections in different populations and from appropriate specimen sites.

2. Indicate that prevalence may vary depending on geographical location, age, sex of population studied, type of test employed, specimen collection and handling procedures, clinical and epidemiological history of individual patients, etc.

F. Limitations of the Test.

List important test limitations and all known contraindications, with references when appropriate. All tests which claim to detect chlamydiae must include at least the following in the Limitations Section, as appropriate for specimen types, unless performance data or corroborated references have been submitted to substantiate that a particular limitation or contraindication does not apply.

1. Test only indicated specimen types. Testing of other specimens types may result in false negative or positive results.

2. Only standard chlamydial cell culture methods should be used in the evaluation of suspected sexual abuse and for other medico-legal indications.

3. The predictive value of a positive test decreases when prevalence decreases. Interpretation of positive results in a low risk patient population should be made with caution. Usefulness of this test has only been established in testing [specimen types] in [high prevalence/symptomatic] populations.

4. Reliable results are dependent on adequate specimen collection. Specimen adequacy can only be assessed by microscopic visualization of columnar epithelial cells in genital tract and conjunctival specimens.

5. Therapeutic failure or success cannot be determined as antigen may persist following appropriate antimicrobial therapy.

6. Interference by gynecological lubricants, spermicides, and other substances has not been established.

7. For those assays using a genus-specific technology, a statement indicating that the assay will not specifically differentiate C. trachomatis, C. pneumoniae, or C. psittaci.

8. Detection of chlamydiae is dependent on the number of organisms (elementary and/or reticulate bodies) present in specimens. This may be affected by specimen collection methods and patient factors such as age, history of STD, presence of symptoms, etc. The minimum detection level of this test may vary according to serovar.

G. Performance Characteristics:

Summarize the data upon which the performance characteristics are based, e.g., clinical sensitivity and specificity compared to cell culture (comparisons to other legally marketed devices may also be presented, if performed); also include summary of reproducibility studies. Positive and negative predictive values should

be based on specific populations sampled for each specimen type (e.g., urine from symptomatic males and urine from asymptomatic males). State the prevalence at each testing site.

1. Present cross-reactivity studies in a tabular form, indicating negative, positive, and borderline/equivocal/indeterminate results for each microorganism.

2. Present limits of detection for all serovars (C. trachomatis-specific assays), or all serovars of C. trachomatis, C. pneumoniae, C. psittaci (genus-specific assays).

3. Summarize within-run and total reproducibility.

4. Present data from comparison studies, using separate categories for different specimen sources. All borderline/equivocal/indeterminate results should be clearly displayed. Discrepancies between test and reference method may be resolved and presented as footnotes or presented in a separate table. Only those specimens which were further evaluated should be represented.

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